DOCKET NO: 278157US0

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
MARIE-CLAUDE GINGRAS, ET AL.	: EXAMINER: BELYAVSKYI
SERIAL NO: 10/021,509	:
FILED: DECEMBER 7, 2001	: GROUP ART UNIT: 1644
FOR: TREM-1 SPLICE VARIANT FOR USE IN MODIFYING IMMUNE RESPONSES	:

REPLY BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

TO THE BOARD OF PATENT APPEALS AND INTEFERENCES:

This reply brief is submitted in response to the Examiner's Answer dated December 18, 2006.

Issue I, Enablement rejection under 35 U.S.C. 112, first paragraph

Claims 1, 3, 5, 11, 15, 16, and 40-42are enabled by the specification and the knowledge in the art meet the requirements set forth in 35 U.S.C. 112, first paragraph

As alleged support for this rejection, the Office contends that the specification 1) does not teach how to effectively modulate any immune response, and 2) does not teach how to use an effective amount of the compounds of this invention. This position appears to be based on the lack of a working example in the specification and the belief that practicing the invention would require undue experimentation.

The disclosure for making the composition consistent with the scope of Claim1 can be found on pages 4-7,11-12, 19, Figures 1 and 4 of the specification as originally filed. Based on the specification and the discussion below, it is clear from reading the Specification that the broad scope of the invention as recited in Claim 1 is supported and enabled.

While there is no working examples in the specification, there is sufficient guidance in the specification and in the art that provide the necessary knowledge for using the claimed methods to effectively modulate an immune response. For example, one need only perform the systemic administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al., *Nature* 410:1103, 2001, and Gibot et al., J Exp Med. 200:1419, 2004, (each previously made of record) as recited in the claims to effectively modulate an immune response. In addition, operability of the claimed methods can be predicted by analogy to the art of Bouchon et al. and Gibot et al.

The Examiner's allegation that undue experimentation would be required to practice the claimed invention based on the speculation that the results of the teaching of the present invention are unpredictable are simply not true. Predictability of the claims in regard to a portion of SEQ ID NO: 2 containing binding activities is verified by the work of Gibot et al. and the whole SEQ ID NO:2 by Bouchon et al. both in animals as mentioned above and explained below.

The fact is that there is a relationship between the structure of the TREM-1 molecules that are members of the Ig superfamily and their respective biological activity. In biology, molecules are described by their respective biological activity. In the case of cellular receptors, their respective biological activity relates to their binding sites. The specificity of TREM-1 is that it is a member of the Ig superfamily of cellular receptors as demonstrated by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 and Ibid. *J. Mol. Biol.* 344:1175, 2004 (of record). The members of this Ig family are characterized by having loop domains folding on each

others. It has been extensively demonstrated over the last three decades that the binding activity of these Ig superfamily receptor molecules is effected by the binding sites located in these disulfide bounded loop domains (see chapter 16 p. 427-29 of Immunology by H. N. Eisen and see Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al—both of record). Although, the work of Kelker et al. could not identify specifically the exact sequence of the binding site in the loop domain, the work of Kelker et al. has confirmed the structure and presence of these loops domains in the different TREM-1 molecules studied. Therefore, the scientific evidence points out that the binding site activity of TREM-1 is within its the loop domain as described in figures 1, 4 and 5 of the present application because of its overall structure and its appertaining to the Ig superfamily of receptors. As cited by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 " TREM-1 (Figure 2(a) and (b), cyan) maintains an overall structure that is homologous to other members of the Ig family," (see page 1240) and " Comparison of the TREM-1 structure to other members of the Ig-V Type fold demonstrates a close structural relationship." (see page 1239)

The Appellant asserts that the objections raised by the Examiner about protein chemistry and unpredictability of efficacy are purely speculative and in this case are demonstrated to be irrelevant due to the simple peptidic nature of the functional binding site of TREM-1sv as mentioned in the specification and demonstrated by Gibot results. Gibot et al. obtained effective immune modulation activity with a small peptide containing only a part of the sequence loop domain being the mouse equivalent peptide of amino acid 103 to 119 of the human sequence (see Figure 4). Thus, compounds having a portion (Gibot et al.), the whole portionor more than the whole portion (Bouchon et al.) of amino acids 36-114 of SEQ ID NO:2 all have a degree of effective immune modulation activity because they contain part of or the whole binding activity site.

As to how to define the dosage, this is routine in the field and certainly cannot be the basis to allege undue experimentation. As mentioned earlier, one can perform the systemic administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al. and Gibot et al as recited in the claims to effectively modulate an immune response. Moreover, as the claimed methods here relate to a therapeutic method some degree of individual variation among patients is inevitable. Medical practitioners routinely prescribe a dose of a therapeutic agent to a patient, observe the response (including any side effects), and modify the dosage or identity of the therapeutic agent depending on the individual patient's response.

The Examiner alleges that the specification does not adequately support that any immune response can be treated with any soluble polypeptide comprising at least a portion of amino acids 1 to 136. The Examiner further basis this assertion because the specification does not provide *in vivo* data. Appellants respectfully submit that the Examiner is incorrect.

The specification clearly asserts that the soluble polypeptides containing the binding site activity can be used to modulate an immune response (e.g., pages 4-7) which is supported by the data discussed in the Declaration of Marie-Claude Gingras, referencing the Bouchon et al publication and the Gibot et al publication noted above. It flows quite clearly from this that the soluble TREM-1 receptor Bouchon et al. utilized uses the teachings of the present invention to show that a soluble TREM- I receptor inhibits cell functions that are activated by TREM-1 (for example, reduced the activity of TREM-1/DAP12 complex, and reduced inflammation). Thus, the soluble TREM-l receptor of Bouchon et al. was acting as a competitive inhibitor, as described by the present application. Moreover, the use of at least a portion of amino acids 1-136 of SEQ ID NO:2 or a polypeptide mimetic thereof such as the polypeptide utilized by Gibot et al. uses the teachings of the present invention to reduce the inflammation.

Appellants assert that the quantity of experimentation needed to be performed by one skilled in the art to establish fine tuning biological efficacy in humans is merely the domain of the FDA and not relevant to claim the present invention. There is sufficient direction or guidance provided in this application for one skilled in the art to produce the claim composition and to use it to modulate the immune response. The methods outlined in the specification provide sufficient directions to enable the modulation of the immune response by administering a compound that decreases the activity of DAP 1 2/TREM- 1 complex, as illustrated by Bouchon et al. and Gibot et al. In light of the data presented by Bouchon et al. and Gibot et al., Appellants assert that the present invention is enabled since one of skill in the art was able to practice the invention without undue experimentation.

With regards to the Examiner's comment about "How can administering the same amount of the same composition of soluble polypeptide with at least a portion of amino acid 1 to 136 of SEQ ID NO:2 or any polypeptide mimetic thereof simultaneously results in two opposite effects, i.e. increase or decrease immune response?" The phenomena can be explained. The nature of the pathogenic ligands to be competed on by TREM-1sv are unknown but evidence suggest they are being produced by different types of pathogens such as some bacterial antigens or bacteria released toxins. Depending of the nature of the pathogenic ligands, they could cause either of an overdrive of the immune response by hyper activation of the macrophages through the TREM-1/DAP12 receptors, or can exert an opposite effect by co-activating the macrophages into a suppressive regulatory mode in which they produce suppressive regulatory factors such as interleukin-10 and TGF-B that will paralyze the immune response. Competing such ligands with TREM-1sv to block them from reaching the TREM-1 receptors on macrophages can either reduce macrophage hyper activation and therefore allow a down-modulation of the immune response, or can prevent

macrophage activation into a suppressive regulatory mode therefore release the immune response from suppression and allowing an up-regulation.

In summary:

1. The mechanisms by which the polypeptide competes for the TREM-1 ligand is described throughout the specification.

2. The structure of different TREM-1 molecules across species have been studied and regardless of their transmembrane region, their ligand binding site is a common conservative region forming a loop binding domain created by a pair of disulfides bridges, one on each end of the loop. (see Kelker et al. and see chapter 16 p. 427-29 of Immunology by H. N. Eisen and see Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al).

3. The enablement of the claimed therapeutic action of the composition having this binding ligand activity is supported by the data in Bouchon et al., and particularly Gibot et al..

4. One can practice the claimed invention because 1) the disclosure for making the composition consistent with the scope of Claim1 can be found on pages 4-7,11-12, 19, Figures 1 and 4 of the specification as originally filed and 2) one can predict the therapeutic efficacy of the composition with TREM-1 ligand activity as long as it contains a portion of the TREM-1SV (see amino acids 1-136 of SEQ ID NO:2) that provides a therapeutic action.

5. One skill in the art can practice this invention based on the competitive inhibition, neutralization or enhancement mechanisms described in the specifications and in the art as practiced by Bouchon et al., and Gibot et al.

6. The sequence of the ligand binding site and its application use for therapy is well disclosed in this application and combined with the common knowledge in the art, a person has all the means to practice this invention to obtain a therapeutic action.

Taken together, the specification coupled with the knowledge in the field demonstrates that the biological activity of immune modulation of all the compounds claimed.

Issue II, Rejection under 35 U.S.C. 102 (e)

Claims 1, 3, 5, 11, 15, 16, and 40-42 are not anticipated under 35 U.S.C. 102 (e) in view of US Patent 6,420,526 or US Patent 6,504,010

A basis of the rejection is the apparent similarity of the sequence SEQ ID NO: 1825 and SEQ ID NO: 2 of this application. The Office's reliance on this is fundamentally misplaced for the following reasons.

(i) The US '010 patent

U.S. '010 describes several hundred sequences, one of which is similar to TREM-1sv strictly for the purpose of treating cancer, generally and lung cancer, specifically. In other words, US '010 describes a hypothetical therapeutic method to treat lung cancer. First, the claimed method of this application is not treating cancer but to modulate an immune response, therefore it is for a different and unclaimed application. Second, the mechanism of action is unclear and no proof or evidence of such a lung cancer therapy using SEQ ID NO 1825 is presented in US '010 because such therapeutic effect is simply non existent and does not fit with the current understanding of how cancer effects the immune response. There is a proposed targeted mechanism of T cell activation but there is no scientific logic to support that mechanism since TREM-1 receptor has been shown not being present on T cells.

Also, the US '010 disclosure does not provide enough specific guidance to specifically use the peptide corresponding to the TREM ligand binding domain and use it for a treatment regimen with the intended purpose of achieving the claimed effect, explicitly or inherently. Therefore, the claims cannot be anticipated by the US '010 patent. In view of the

above, there can be no question that the Office's rejection based on US '010 is not sustainable and should be reversed.

(ii) The US '526 patent

Similarly, the rejection based on US '526 is based on an alleged inherent property of SEQ ID NO 478.

US Patent 6,420,526 is very vague patent. The '526 patent describes a sequence with no details in the specifications on which sequence of the molecule has a function. Functions are associated with translated proteins not with a EST DNA sequence. US Patent 6,420,526 is a multiple EST sequence patent (186 all together) containing the sequence 159 that is the subject of this objection. Sequence 159 contains 6 paragraphs for a total of a little over one page. The description in patent 526 suggests a potential use to regulate the immune response but does not describe enough to reduce to practice without undue experiments such as which part of the molecule is relevant to practice the invention. To the contrary of the present application, patent 526 description is 1) minimal with a lack of description on the molecule to use and its functional sites for someone to reduce this invention to practice. 2) There is no guidance or working evidence presented to support the rejection. 3) The present application claims are not directed to an EST sequence and related molecules as in U.S. '526 but a function of the SEQ NO:2 molecule to modulate the immune response to treat autoimmune diseases and septic shock, which is not at all described nor reasonably ascertainable from the teachings of US '526.

Fundamentally, US '526 lacks any real disclosure that would put into the public's possession the claimed methods. US '526 merely describes an expressed sequence tag (EST) DNA sequence, among many others, including a matching sequence of TREM-1sv. US '526 does not indicate which one or which combination of the sequence SEQ ID NO 478 being

presented in seven different epitopes, must be used to produce a polypeptide usable as a protein therapeutic to modulate an immune response and whether it is an up-modulation or a down-modulation. Consequently, how can one anticipate a complete therapeutic method from such a lack of information unless it refers to the present invention? The present invention fulfills the need by clearly defining the use of TREM-1sv as a protein therapeutic for down-regulating the immune response.

As the US '526 disclosure does not set forth a treatment regimen with the intended purpose of achieving the claimed effect, explicitly or inherently, the claims cannot be anticipated by the US '526 patent.

In view of the above, there can be no question that the Office's rejection based on US '526 is not sustainable and should be reversed.

Issue III, Rejection under 35 U.S.C. 112, first paragraph, New Matter rejection

The limitations of Claims 1, 3, 5, 11, 15, 16, 40 -42 do not constitute new matter

The examiner asserts that the new claims represent a departure from the application as originally filed by missing clear support for " a composition comprising at least a portion of amino acid 1 to 136..."

Support for the phrase in claims 1 and 3 of "any soluble polypeptide having at least a portion of amino acid 36 to 114 of SEQ ID NO:2, the whole portion ... or more than the whole portion..." is presented in great detail in the specification at paragraphs 55, 59, 60, 72, 73, 75, 76, 78, 80 in which "...present invention also includes, but is not limited to variants or biological function equivalents of the TREM-1 splice variant..." "...variants and further variants with deletion and or addition in any combination..." are presented and thus referred to in the claims as being "...any soluble polypeptide having at least a portion of amino acid 36 to 114 of SEQ ID NO:2, the whole portion ... or more than the whole portion...".

Claim 42 is supported at paragraph [0031]

Appellants respectfully request that the rejection be withdrawn.

An Oral Hearing request is concurrently being filed.

Respectfully submitted,

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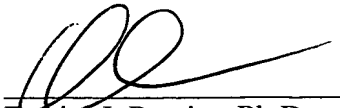
Norman F. Oblon



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CASE SPECIFIC POWER OF ATTORNEY

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM and STATEMENT UNDER 37 CFR 3.73(b)		
	Application Number	10/021,509
	Filing Date	December 7, 2001
	First Named Inventor	Marie-Claude GINGRAS, et al.
	Title: TREM-1 SPLICE VARIANT FOR USE IN MODIFYING IMMUNE RESPONSES	
	Attorney Docket Number:	278157US0

I hereby appoint:

■ Practitioners associated with the Customer Number 22850

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

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■ The address associated with the above-mentioned Customer Number.

I am the:

■ Assignee of record of the entire interest. See 37 CFR 3.71.

GenePrint Corporation (Name of Assignee), a Corporation (Type of Assignee, e.g., corporation, partnership, government agency, etc.)

■ States that it is the assignee of the entire right, title, and interest. A copy of the assignment is attached.

SIGNATURE OF ASSIGNEE OF RECORD

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Eugene Roussel — Signature — July 28, 2006 — Date

Eugene Roussel — Printed or Typed Name — 713-988-3003 — Telephone Number

CEO — Title

THIS FORM CAN ONLY BE SIGNED WHERE THERE IS ONLY A SINGLE ASSIGNEE

ASSIGNMENT

COPY

WHEREAS, Marie-Claude Gingras of 8027 Oakington Drive, Houston, Texas 77071 and Judith F. Margolin of 5326 Dumfries, Houston, Texas 77096, are the exclusive joint owners, by assignment, of the application for letters patent of the United States of America Application No. 10/021,509 filed December 7, 2001; and

WHEREAS, GenePrint Corporation of 8027 Oakington Drive, Houston, Texas 77071 (hereinafter referred to as "ASSIGNEE"), is desirous of acquiring the entire right, title and interest in and to said application for letters patent, the invention described therein, and in and to any and all Letters Patent that maybe granted therefor in the United States and its territorial possessions;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00) and other valuable consideration, the receipt of which is hereby acknowledged, Marie-Claude Gingras and Judith F. Margolin by these presents do sell, assign and transfer unto said ASSIGNEE the entire right, title and interest for the territory of the United States of America in and to the aforesaid application for letters patent, the invention described therein and in and to any and all Letters Patent which may be granted therefor and in and to any and all divisions, continuations, reissues, substitutions and renewals thereof.

Marie-Claude Gingras and Judith F. Margolin hereby authorize and request that the Patent Office in the United States and its territorial possessions to issue any and all of said Letters Patent, when granted to said ASSIGNEE as the assignee of the entire right, title and interest, for the use and behoof of said ASSIGNEE, its successors and assigns, to

the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by us had this Assignment and sale not been made.

Date: March 1st, 2006 By: _____
Marie-Claude Gingras

Date: March 1, 2006 By: _____
Judith F. Margolin